THE HONORABLE ROBERT S. LASNIK

UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF WASHINGTON
AT SEATTLE

MARY CHANDLER AND MICHAEL CHANDLER, husband and wife, Plaintiffs, v. **GREENSTONE LTD., et al.** Defendants.	**Case No. 04-1300RSL** **PLAINTIFFS' RESPONSE IN OPPOSITION TO DEFENDANTS' MOTIONS *IN LIMINE***

Plaintiffs respond to each of defendants' motions *in limine* below.

RESPONSES TO DEFENDANT WYETH'S MOTIONS *IN LIMINE*

W1. Marketing Evidence.

Wyeth conflates several distinct categories of documents under the "marketing" rubric to argue for the wholesale exclusion of probative evidence. Specifically, Wyeth's definition of "marketing evidence" broadly includes not only advertisements and promotional brochures, but also documents concerning the strategies the company employed to influence physicians and the public to believe that E+P had no breast cancer risk and conferred significant cardiovascular benefits. Plaintiffs do not intend to introduce advertisements or marketing brochures for the purpose of arguing that Mrs. Chandler and her doctors saw and relied on them. But some documents which Wyeth characterizes as "marketing" are admissible for other probative reasons.

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Thus, the Wyeth "marketing" documents plaintiffs will present at trial are relevant to show: 1) Wyeth's conduct upon receiving notice of FDA violations and potential breast cancer risk; 2) causation; and 3) Wyeth's influence of Mary Chandler's prescribing physician to prescribe E+P for cardiovascular and other benefits. Several courts, including the MDL, have admitted "marketing" documents for these very purposes.

A. The evidence is probative of Wyeth's negligent conduct.

Wyeth's main argument is that documents not seen by plaintiff Mary Chandler or her doctor are *per se* irrelevant. Wyeth ignores plaintiffs' burden at trial: Plaintiffs must prove: (a) Wyeth had a duty to monitor and test E+P in light of the red flags or safety signals that arose with these drugs; (b) Wyeth failed to adequately study or "test" its drugs; (c) Wyeth provided inadequate warnings as a result of the lack of studies; (d) Wyeth deliberately downplayed and minimized any study findings that showed a breast cancer risk and took active steps to neutralize critics of E+P; (e) Wyeth's inadequate risk information led plaintiff and her prescribing physicians to opt for E+P for nearly 11 years; and (f) E+P was a substantial factor in the development of plaintiff Mary Chandler's breast cancer.

The fact that Mary Chandler and her doctors never "relied upon" so-called marketing documents is beside the point. Wyeth saw to it that neither Mrs. Chandler nor her physicians would have any occasion to see the internal documents that prove (a) through (d). So, naturally, neither Mrs. Chandler nor her doctors were privy to internal memoranda revealing that Wyeth disregarded breast cancer information, ignored dozens of red flags, scuttled breast cancer research proposals, and deployed its PR machine to discredit studies that did manage to get published because Wyeth knew such studies would likely condemn E+P and hurt sales.

Marketing documents demonstrate that Wyeth promoted E+P for cardiovascular benefits despite FDA's repeated admonitions not to do so, because this was an "unproven or yet-to-be-proven benefit." [1] Wyeth's correspondence regarding Wyeth's marketing activity is direct

[1] Ex. 1, PX 194, Internal correspondence from S. Sasson (4/26/92).

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evidence of Wyeth's knowledge and acknowledgment of its duty to study as well as its breach of that duty. And as explained below, plaintiff's physicians were universally influenced by Wyeth's pervasive "cardiac benefit" message. Marketing documents also reflect Wyeth's reaction to concerns raised in the scientific community about potential breast cancer risk. Instead of following up with studies of its own, Wyeth waged an aggressive PR campaign to "dismiss and distract" physicians and patients.[2] Wyeth's "Myths and Misperceptions" campaign sought to downplay negative research findings by convincing doctors and patients that breast cancer risks were illusory and greatly outweighed by unproven benefits.[3]

B. Many "marketing" documents are relevant to causation.

Central to plaintiffs' causation theory is that women with significant menopause symptoms have lower than average levels of estrogen in their bodies, making their breast cancer risk lower than average, but they can develop hormone-dependent breast cancer when the cancer is fed by exogenous (external) hormones such as E+P. In every trial to date, however, Wyeth denies that its drug played any role in causing plaintiff's breast cancer and that there is no such thing as "estrogen deficiency." Wyeth contends that the plaintiff's own production of estrogen was sufficient to cause her cancer. Wyeth's marketing materials flatly contradict this argument:

> Estrogen deficiency can occur naturally during menopause or surgically (when both ovaries are removed). No matter how it occurs, estrogen deficiency is accompanied by many physical symptoms… In the short term, vasomotor symptoms, including hot flashes and night sweats, are generally the first changes.[4]

Plaintiffs and their experts are entitled to rely on these admissions to counter Wyeth's made-for-litigation theory that estrogen deficiency has nothing to do with menopausal

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[2] Ex. 2, PX 349 – Buchalter handwritten notes

[3] Ex. 3, PX 427, Ex. 4, PX 7422A.

[4] Ex. 5, PX 6093, Wyeth-Ayerst Women's Health Issues & Hormones, 1995 at 1-3. Ex. 6, McNagny, *Prescribing Hormone Replacement Therapy for Menopausal Symptoms*, 131(8) Ann INTERN MED (Oct. 19, 1999) (article sponsored by Wyeth).

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symptoms. The Eighth Circuit expressly found these marketing admissions probative. "Although Wyeth presented evidence disputing this association, the factual basis of an expert opinion is assessed by the jury… and the jury may have been persuaded by Wyeth's own documents asserting a link between hormone deficiency and uncomfortable menopausal symptoms." *In re Prempro Prods. Liab. Litig.*, 586 F.3d 547, 556 n. 12 (8th Cir. 2009), *cert. denied*, 130 U.S. 3467 (Jun. 21, 2010).

C. Plaintiff's prescribing doctor was influenced by Wyeth's marketing materials.

Wyeth suggests that because Mrs. Chandler's physicians did not rely on any particular promotional pieces, the company could not possibly have influenced their decisions to prescribe E+P. Again, Wyeth misses the point. Wyeth's most successful marketing strategy did not depend on brochures and journal ads. Instead, it cleverly influenced women's doctors by sponsoring continuing medical education ("CME") seminars and other "pipelines," including medical organizations such as the American College of Obstetricians and Gynecologists 9"ACOG") and National Menopause Society ("NAMS"). Wyeth mobilized assistance from its allies in these "third party" groups and used them as a conduit to spread its marketing messages, issuing "scientific" statements defending E+P.[5] Wyeth devised CME programs whose goal was "to assist primary care providers in discussing current research findings on breast cancer risk and HRT with their female patients."[6] The physicians who read CME materials had no way of knowing that Wyeth orchestrated the information.

The physicians' testimony suggests that Wyeth's strategy worked. Dr. Velcoff started Mrs. Chandler on E+P in 1990.[7] Dr. Velcoff believed that E+P protected the heart and prevented osteoporosis. This view widely held. She got this information from medical journals and the

[5] Ex. 7, PX 345 3/27/96 memo to Buchalter et al re Cummings Study.

[6] Ex. 8, PX 7298, Women's Health in Primary Care Oct. 2001.

[7] Ex. 9, Velcoff Dep. at 16.

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label.[8] Dr. Velcoff also relied on her colleagues in the Ob/Gyn community and on continuing medical education seminars. In fact, Dr. Velcoff attended CMEs sponsored by drug companies.[9] Dr. Velcoff was concerned because Mrs. Chandler was at risk for osteoporosis.[10] She had meetings with drug sales representatives, but she doesn't recall meeting Wyeth reps specifically.[11] Dr. Velcoff was not aware that E+P increased the risk of breast cancer; otherwise, she wouldn't have taken it herself.[12] Likewise, Cathie Gurgel, N.P. believed that HRT was "good for your heart, all sorts of things."[13]

As the court in *Barton v. Wyeth* held, Wyeth's marketing materials were properly allowed because the evidence was relevant to the jury's determination of Wyeth's liability. Even though the doctor in that case did not purport to rely on specific documents, his prescribing habits and those of his colleagues were the generally accepted standard of care prior to the WHI study. "Therefore, logic demands some explanation for the source of this belief. The marketing materials circumstantially provide such relevant evidence."[14] Other courts agree.[15]

The bottom line is that the evidence must be evaluated piece by piece and cannot be categorically excluded as "marketing evidence." It is misleading to suggest that there should be a single criterion for evaluating the admissibility of all documents Wyeth believes fall within the definition of "marketing."

W2. <u>Ghostwritten Articles.</u>

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[8] *Id.* at 33.

[9] *Id.* at 50, 71.

[10] *Id.* at 26-27.

[11] *Id.* at 53-54.

[12] *Id.* at 31.

[13] Ex. 10, Gurgel Dep. at 48:24-49:12.

[14] Ex. 11, Order, *Barton v. Wyeth,* (Phila Ct. Comm. Pl. Jan. 29, 2010) at 48.

[15] Ex. 12, Order, *Singleton v. Wyeth,* Jan. Term 2005, No. 02885 (Phila Ct. Comm. Pl. Dec. 29, 2009); Ex. 13, Order, *Foust v. Wyeth,* June Term 2004, No. 04606 (Phila. Ct. Comm. Pl. Jan. 22, 2010); Ex. 14, Order, *Simon v. Wyeth*, No. 4229 (Phila. Ct. Comm. Pl. Apr. 16, 2007); Ex. 15, Order, *Esposito v. Wyeth*, No. 04606 (Pinellas Cnty, Fla. Jun. 25, 2010).

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Wyeth's objection to ghostwriting evidence rests on three separate premises: First, it disapproves of the term "ghostwriting" itself, claiming it is a legitimate activity. Second, Wyeth maintains that ghostwriting evidence is prejudicial and that courts generally exclude it. And third, Wyeth contends it is irrelevant because plaintiff's doctors did not "rely" on ghostwritten materials. Each of these arguments lacks merit.

1. The fact that ghostwriting is "common" doesn't make it right.

Wyeth defends its practice of ghostwriting medical articles on the grounds that "everyone does it," and in any event, it isn't illegal. Nevertheless, the act of writing and publishing studies under a false *nom de plume* without disclosing the true author's identity has long been widely scorned. As early as the 1940s, the United State Supreme Court wrote in dicta:

> Ghost-writing has debased the intellectual currency in circulation here and is a type of counterfeiting which invites no defense. Perhaps this Court renders a public service in treating phantom authors and ghost-writers as legal frauds and disguised authorship as a deception.

Kingsland v. Dorsey, 338 U.S. 318, 324 (1949).

Indeed, it is this very activity that prompted journalists and the scientific media to intervene in the MDL to air Wyeth's ghostwriting to the public.[16] Disclosure of Wyeth's dirty secret led to an outcry in the scientific community. As a consequence, some journals have implemented policies banning submissions by authors found to engage in ghostwriting.[17] It also led to a body of research showing that medical ghostwriting has a profound influence on the prescribing habits among physicians, thus refuting Wyeth's claim that this pervasive tactic has

[16] Ex. 16A, Order, MDL Dkt No. 4:03-CV-1507-WRW, Doc. No. 2120 (E.D. Ark. Jul. 24, 2009).

[17] *See, e.g.*, Ex. 16B, *Commentary, European Medical Writers Association (EMWA) guidelines on the role of medical writers in developing peer-reviewed publications*, 21(2) Current Medical Research and Opinion 317 (2005). Several medical journals, including PLoS, have adopted these guidelines in response to revelations of Wyeth's ghostwriting activities.

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"no nexus" to any plaintiff's physician.[18] Legal scholars have likewise condemned ghostwriting and are calling for the imposition of legal liability for committing a fraud on the court and academic institutions.[19] Even if we were to accept Wyeth's argument that it didn't violate any law, its conduct is generally viewed as unreasonable and thus, negligent.

2. Ghostwriting evidence is routinely deemed admissible.

Other courts in the hormone therapy litigation, including trial courts in Nevada, New Jersey and Pennsylvania, have rejected Wyeth's similar arguments, holding that ghostwriting evidence is relevant and admissible.[20] Wyeth's ghostwriting documents have also been admitted in three federal bellwether trials before the MDL court. *In re Prempro Prods. Liab. Litig.*, 586 F.3d at 557. Judge Robert Perry, coordinating judge for Nevada hormone therapy cases, explained the significance of this evidence in his post-trial order in *Rowatt v. Wyeth*:

> Here, there was substantial evidence from which the jury could conclude that Wyeth knew that its product could cause breast cancer, that it intentionally failed to conduct adequate tests, ***that it financed and manipulated scientific studies, and sponsored articles in professional and scientific journals that deliberately minimized the risk of cancer while over-promoting certain benefits*** and citing others which it knew to be unsubstantiated.[21]

The Nevada Supreme Court affirmed Judge Perry's order. It found that ghostwriting evidence adequately formed the basis for the court's approval of the jury's award for both compensatory and punitive damages. "…Published under independent doctors' names, the 51

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[18] Ex. 17A, Spielmans, Parry, *From Evidence-Based Medicine to Marketing-based Medicine: Evidence from Internal Industry Documents,* 7 BIOETHICAL INQUIRY 13 (2010).

[19] Ex. 17B, S. Stern, T. Lemmens, *Legal Remedies for Medical Ghostwriting: Imposing Fraud Liability on Guest Authors of Ghostwritten Articles,* 8(8) PLos Medicine (Aug. 2011).

[20] *See, e.g.,* Ex. 18, Order, *Barton v. Wyeth* at 19 (Phila. Ct. Comm. Pl. Jan 29, 2010); Ex. 19, Trial Tr.at 11-28, *Kendall v. Wyeth* (Phila. Ct. Comm. Pl. Nov. 3, 2009 pm), and. 91-96 (Nov. 5, 2009 a.m.); Ex. 20, Trial Tr. 55:3-80:3, *Singleton v. Wyeth* (Phila. Ct. Comm. Pl. Feb. 3, 2010 a.m.); Ex. 21, Trial Tr. 100:17-23, *Foust v. Wyeth* (Phila. Ct. Comm. Pl. Feb. 4, 2010)

[21] Ex. 22, Order, *Rowatt v. Wyeth* No. CV04-01699 (Washoe Cnty, Nev. Feb. 19, 2008) at 3 (emphasis added).

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[Wyeth sponsored] ghostwritten medical articles touted the benefits of hormone replacement therapy while minimizing the breast cancer risks." *Rowatt v. Wyeth*, 244 P.3d 765, 772 (Nev. 2010). The court further found that Wyeth's deliberate effort to undermine scientific reporting justified damages. "Over the years, Wyeth organized task forces to contain any negative publicity about hormone therapy and breast cancer. Wyeth's strategy to undermine scientific studies linking an increased risk of breast cancer to estrogen-progestin hormone therapy included ghostwriting multiple articles." *Id.* at 784.

In upholding the jury verdict in *Scroggin v. Wyeth*, an MDL bellwether trial, the Eighth Circuit directly addressed the argument Wyeth makes here, that ghostwriting is a legal, commonplace and legitimate activity. The court described at length an example of Wyeth's ghostwriting practices that took place in 2000. The end product enabled Wyeth's own scientific director to facilitate the absorption of the ghost-written article (favorable to HRT) "into the collection of reliable medical data." *In re Prempro*, 586 F.3d at 557.

Outside the hormone therapy arena, several courts have similarly held that evidence of drug companies' ghostwriting activities supported a jury award for plaintiffs. *See, e.g., Proctor v. Davis*, 682 N.E. 2d 1203, 1215 (Ill. App. Ct. 1997) (noting that defendants' ghostwriting "should be neither countenanced, encouraged nor condoned."); *Giles v. Wyeth*, 500 F. Supp. 2d 1063, 1064 (S.D. Ill. 2007) (denying summary judgment on plaintiff's failure to warn claim based in part on evidence that Wyeth had "utilized material misrepresentations to promote and market its drug via the practice of 'ghost writing' scientific articles for publication under the names of prominent academic 'authors'"); *Tucker v. SmithKline Beecham Corp.*, 701 F. Supp. 2d 1040, 1048 (S.D. Ind. 2010) (liability expert's opinion was admissible based in part on evidence of ghostwritten scientific articles which led to exaggeration of benefits of drugs and concealment of their risks); *Williams v. Philip Morris, Inc.*, 48 P.3d 824, 834 (Or. 2002), *vacated and remanded on other grounds*, 540 U.S. 801 (2003) (tobacco company disseminated messages to public by "influencing the conduct of apparently neutral articles and cultivating "opinion

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leaders" who would convey their message). Plaintiffs do not contend that Wyeth did not have the right to publish scientific articles. What plaintiffs take issue with is Wyeth's failure to disclose its involvement in writing them.

3. Plaintiff need not prove that her prescribing doctors "relied" on ghostwritten articles.

Plaintiffs have alleged claims of negligence and design defect. They have not alleged fraud, and therefore, they need not prove the elements of a fraud claim. Further, defendants miss the point of the ghostwriting evidence: it reflects Wyeth's culpable conduct. Instead of following up with proper studies and warning about breast cancer risk, Wyeth chose to suppress the information and distort the risk/benefit profile of its HRT drugs by polluting the scientific literature to give the medical community the overall impression that HRT's benefits were great and breast cancer risks were minimal. For example, Dr. Velcoff, one of Mrs. Chandler's prescribing doctors, had no idea that companies like Wyeth engaged in ghostwriting, so she couldn't have known if what she was reading was sponsored by a drug company.[22] Ghostwriting is simply one piece of Wyeth's consistent pattern of deception. A jury should be permitted to consider it, along with other evidence, in assessing Wyeth's negligence.

W3. Testimony of Bruce Aaseby

Wyeth's claims plaintiffs have no right to call its former sales representative, Bruce Aaseby, to trial. To bolster its argument, Wyeth relies on selected testimony of Cathie Gurgel, a nurse practioner at Kaiser who refilled Mrs. Chandler's HRT prescriptions for a short time. Wyeth contends Ms. Gurgel testified that she didn't rely on any sales representatives in making treatment decisions for her patients. This proves nothing. On the contrary, Ms. Gurgel did not recall having *any* discussions with drug company sales reps regarding HRT.[23] At most, Ms. Gurgel's self-serving testimony on this point is pure speculation.

Although Wyeth's sales rep Bruce Aaseby may have called on Ms. Gurgel just once, he

[22] Ex.09, Velcoff Dep. at 71:25-72:18.

[23] Ex. 10, Gurgel Dep. at 76:11-16.

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also called on physicians at the Kaiser facility, including obstetrician/gynecologists, whom Ms. Gurgel consulted with "several times a day" for guidance on questions concerning drugs and drug labeling.[24] Plaintiffs are entitled to ask Mr. Aasbey to tell the jury what he told these physicians – upon whom Ms. Gurgel relied – about the risks and benefits of HRT. Ms. Gurgel further testified that the consensus among her colleagues and her in 1998 was that HRT had all sorts of benefits and was even good for the breast:

> Q: Okay. And when you – and understanding you don't have a specific recollection for Ms. Chandler, but those medications, Premarin and Medroxyprogesterone, why are they prescribed to women such as Ms. Chandler?
>
> A: Well, back in that day, we gave hormones to women for – we thought it was good for – we thought it was good for breast health. We thought it was good for your brain. We thought it was good for your heart, all sorts of things.
>
> I can recall thinking, wow, maybe I'm going to have to take these hormones, because that's – and I remember that specifically, that hormones were touted as being good for your, you know, brain, your breast, your – all sorts of things.[25]

By law, these alleged benefits could not be "touted" in the drug label or the PDR. Logic and a basic reading of Wyeth's sales and PR strategies suggests that this "understanding" by Ms. Gurgel and her colleagues of the risk/benefit profile came from information provided by Wyeth. What Wyeth trained Mr. Aaseby and other sales representatives to tell the physicians at Kaiser concerning HRT is also a fertile area for cross-examination at trial. Furthermore, it is disingenuous for Wyeth to argue that the testimony of its own former employee would be "irrelevant, unfairly prejudicial, and an unnecessary side show." Presumably, Wyeth continues to have control over this witness. In fact, because Wyeth refuses to make its current employee witnesses available for trial, Mr. Aaseby, who lives in Washington, is the only Wyeth witness

[24] Ex. 10, Gurgel Dep. at 71:8-72:13.

[25] Ex. 10, Gurgel Dep. at 48:24-49:12.

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plaintiff can call to testify in person. If Wyeth is concerned that Mr. Aaseby will portray it in a negative light, it is free to examine him when plaintiffs' cross-examination is completed.

Wyeth also misrepresents how other courts have ruled on the admissibility of sales rep testimony. In keeping with its usual pattern, Wyeth only discloses the isolated rulings that go its way. Specifically, Wyeth clings selectively to rulings in *Hines.* Wyeth will not cite the overwhelming number of contrary decisions allowing the testimony of Wyeth's sales representatives. Sales representatives have testified in person or via videotape in almost every trial. This testimony is decidedly not the "side show" defendants claim.

W4. Sales Representatives Who Did Not Call on Mrs. Chandler's Prescribers

Despite defendant's protestations to the contrary, testimony of other Wyeth sales representatives is relevant to establish that the promotion of off-label benefits reflected the company's policy and not the actions of "rogue" agents. At the heart of Wyeth's liability is its decision to avoid investing resources in studies to assess the breast cancer risk from E+P; instead, it chose to use its resources to market its drugs aggressively for unapproved uses. As part of its overall PR strategy, Wyeth devoted its efforts to training sales staff to promote unproven benefits and downplay the risk of breast cancer. This conduct is found in the call notes of *hundreds* of sales representatives throughout the country and in the testimony of former Wyeth employees whom plaintiffs will call at trial.

Defendants fail to acknowledge that several courts in the HRT litigation have denied Wyeth's similar motions and allowed plaintiffs to present this testimony.[26] In *Rowatt v. Wyeth,* for instance, the court permitted plaintiffs to introduce the testimony of Brett Hendricks, a former Wyeth sales representative, who had not called on the plaintiffs' prescribing doctors.[27] Mr. Hendricks' testimony is important, because it shows that collectively, Wyeth's sales force

[26] *See, e.g.*,Ex. 23, Order, *Deutsch v. Wyeth,* MID-L-0998-06 MT (Middlesex Cnty. Super. Ct. N.J. Jun. 14, 2007).

[27] Ex. 24, Tr. Beginning at 551, *Rowatt v. Wyeth* (Sept. 12, 2007) (entirety of testimony not included).

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received the same marketing directive. All sales representatives received the same training manuals.[28] Mr. Hendricks attended the Prempro "launch" meeting, along with thousands of other sales representatives, received extensive training on how to market Prempro to physicians. From "[d]ay one, we were taught that this combination should be used until the woman passes away. This is a lifelong commitment. And we recognized that if a patient stopped therapy after a short period of time, then that [*sic*] those dollars were lost. If they continued to take it – then it would continue to be profitable."[29]

As to the purported benefits of E+P, Mr. Hendricks testified that Wyeth trained sales reps to promote E+P for heart and cognitive benefits – both unapproved by FDA.[30] As he explained, "The directions from our management would be clearly to discuss these benefits."[31] Wyeth further instructed its sales reps to "redirect" the conversation away from risks to "basically emphasize the benefits of the product and that these benefits far outweigh any disadvantage that could be there."[32] In addition, "[t]he training emphasized that we downplay the breast cancer issue."[33] Mr. Hendricks' testimony is particularly striking – and directly relevant to the issues in this case – because it shows Wyeth's strategy worked in this case. Mrs. Chandler's prescribers believed that HRT had these very same benefits and very little risk.

Regardless whether these sales representatives ever met with plaintiffs' prescribers, their testimony is relevant to the issue of how Wyeth instructed its staff to market E+P to all physicians, including the doctors in this case.

W5. <u>Wyeth's Inclusion of an Endometrial Cancer Warning in the Premarin Label</u>

Defendants vigorously oppose this evidence precisely because it is so powerful. The

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[28] Ex. 24 at 566:11-20.

[29] *Id.* at 602;24-603:9.

[30] *Id.* at 638:13-640:9.

[31] *Id.*at 643:5-644:18.

[32] *Id.* at 645:6-16.

[33] *Id.* at 615:2-616:18.

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parallel between the Premarin induced endometrial cancer epidemic in the 1970s and the subsequent Premarin/Provera induced breast cancer epidemic is obvious. Wyeth's deliberate refusal to learn its lessons from the first hormone drug disaster led directly to the second one. It goes directly to the heart of Wyeth's liability in this case.

A. Background

Wyeth introduced Premarin to the market in 1942.[34] Premarin ("E") is made of conjugated estrogens, derived from horse urine. The product went practically unnoticed until the publication in 1965 of a book called *Feminine Forever*. That book promised menopausal women that Premarin was a fountain of youth that would restore a woman's femininity and make her more palatable to her husband. Prescriptions for Premarin soared. But just as Premarin sales peaked in the mid-1970s, Wyeth got a wake-up call. A study of cancer databases by Dr. Donald Austin and colleagues showed a disproportionate increase in the incidence of uterine (endometrial) cancer among older affluent, white women in the United States, which corresponded to the rise in post-menopausal estrogen prescriptions.[35] Two epidemiologic case-control studies quickly confirmed that estrogens used for menopausal hormone therapy were to blame for this new epidemic of uterine cancer.[36] These three studies – none of them funded by Wyeth – were presented at a formal hearing to the FDA, which led the agency to require new "black box" class labeling to warn of the hormone-dependent endometrial (uterine) cancer risk. As a result, the FDA determined Premarin should be indicated only for use in women without a uterus. At the hearing, the study authors testified that their research was inexpensive to do,

[34] Drs. Austin, Parisian, Blume and/or Patsner will testify about the history of Wyeth's hormone therapy drugs.

[35] Ex. 25, M2065, N. Weiss, D. Dzekely, D. Austin, *Increasing incidence of endometrial cancer in the United States*, 294, No. 23, NEW ENG. J. MED. 1259-76 (Jun. 3, 1973)

[36] Ex. 26, M2046, D.C. Smith et al., *Association of exogenous estrogen and endometrial carcinoma*, 293, No. 23, NEW ENGL. J. MED. 1164-67 (Dec. 4, 1975); Ex. 27, T.M. Mack et al., *Estrogens and endometrial cancer in a retirement community*, 294, No. 23, NEW ENG. J. MED. 1262-67 (Jun. 3, 1976).

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which prompted a reporter to question why Wyeth had not conducted these studies sooner.[37]

Revelations that its estrogen drug caused a hormone-dependent cancer epidemic should have prompted Wyeth to warn physicians not to prescribe Premarin to women with an intact uterus. Instead, Wyeth responded to the news by minimizing the findings of the three epidemiological studies. In a "dear doctor" letter dated December, 1975, Wyeth assured physicians that the evidence presented to the FDA was "controversial."[38] Wyeth told doctors that when used according to directions, any potential risk of Premarin was "minimized," and that "women may continue to receive the proven benefits of estrogen replacement therapy."[39]

Wyeth's letter angered the FDA. The FDA told Wyeth that it considered the letter to be a misrepresentation, finding that it was "warped in tone" and was "intended to obfuscate the issues rather than to highlight new information related to risk.[40] The agency further rebuffed Wyeth for not providing a sound medical and scientific response to such important information. The FDA was emphatic that a manufacturer – particularly an industry leader like Wyeth – has the duty to take responsibility for scientific data and to monitor the safety of its drugs:

> Any drug firm, Ayerst in this case, should know its drug, be aware of positive developments regarding its use and be responsible. The FDA is not impressed with the passive mode displayed by Ayerst Laboratories in this case. An NDA labeling supplement with proposed new labeling and proposed research plans is in order from Ayerst.[41]

In 1982, a follow-up study by Dr. Austin found that the rapid appearance and disappearance of the uterine cancer epidemic was evidence that Premarin was a promoter of hormone-dependent cancers. In other words, Premarin quickly stimulated harmless pre-

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[37] Ex. 28, Transcript of Obstetrics and Gynecology Advisory Committee hearing, Dec. 16, 1975, at p.44.

[38] Ex. 29, Letter from John B. Jewell, M.D., Wyeth, to doctors (Dec. 1975)

[39] *Id.*

[40] Ex. 30, FDA memorandum of conference with Wyeth, 1/12/76, at p.3.

[41] *Id.*

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cancerous lesions into full-blown, potentially lethal invasive cancers.[42] By then, Wyeth had redeemed its Premarin franchise from financial doom by marketing it for use with progestins (MPA) because studies showed that adding synthetic progestins would reduce the risk of endometrial cancer. But Wyeth also became increasingly aware that the endometrial cancer studies for E alone had implications for the role of E+P in causing breast cancer by the *same* "promotion" mechanism. This should have alarmed Wyeth because MPA was known to cause cellular proliferation and breast tumors in animals, alone and combined with estrogen. But rather than conduct population and case-control studies like the ones conducted by Dr. Austin and his colleagues (which could have been completed in two to three years), Wyeth embarked on a "dismiss and distract" campaign to suppress breast cancer studies, play up the benefits of HRT and downplay concerns about breast cancer risk.

B. The endometrial cancer lesson is highly relevant to Wyeth's conduct in causing Mrs. Chandler's cancer.

Wyeth's aggressive promotion of E+P over the next two decades continued unabated. But despite its well-orchestrated efforts to suppress research, a growing number of studies suggested that E+P caused hormone-dependent (ER+) breast cancers via a "promoter" effect, just as E alone promoted the growth of endometrial cancers. In 2002, the investigators suddenly halted the Prempro (E+P) clinical trial arm of the WHI study because they found an alarmingly high rate of breast cancer in women randomized to the drug. Beginning in 2003, researchers discovered a startling trend: The number of hormone-dependent (ER+) breast cancers in postmenopause-age women fell dramatically. This decline also mirrored a similar drop in prescriptions for E+P.[43] These studies all concluded that the rise and fall in ER+ breast cancers,

[42] Ex. 31, M0133, D. Austin and K. Roe, The decreasing incidence of endometrial cancer: public health implications, 72 AM J PUB HEALTH, 65-68 (Jan. 1982)

[43] Ex. 32, M4743, Ravdin et al., *The Decrease in Breast Cancer Incidence in 2003 in the United States*. N ENGLAND J MED 356;16:1670-1674; Ex. 33, M4586, Clarke CA, et al., *Recent declines in HT utilization and breast cancer incidence*., J CLIN ONCOL. 2006 Nov 20;24(33):e49-50.; Ex. 34, M4770,

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which corresponded to a matching rise and fall in E+P prescriptions, was due to E+P use. The pattern of E+P use that lead to the epidemic of ER+ breast cancer is a repeat of the E-induced epidemic of hormone-dependent uterine cancers two decades earlier.

The breast cancer epidemic incited by Wyeth could easily have been avoided. Wyeth acknowledged that observational studies were the appropriate design for assessing and measuring cancer risk. In fact, Wyeth funded at least one case-control study on Premarin and uterine cancer and another on Premarin and breast cancer.[44] It was feasible and inexpensive for Wyeth to conduct these studies. Beginning in the 1980s, Wyeth could have monitored breast cancer rates in the population from cancer registry data, as Dr. Austin had done, and followed up with case-control studies. Wyeth repeatedly turned down proposals by other researchers to conduct breast cancer studies on E+P.

The Eighth Circuit recognized the relevance of the endometrial cancer disaster. The court spent several paragraphs explaining its importance. *In re Prempro Prods. Liab. Litig.,* 586 F.3d 547, 554-555 (8th Cir.2009). Indeed, the court compared "Wyeth's Reaction to Estrogen Replacement Therapy Being Linked to Endometrial Cancer" to "Wyeth's Reaction to Hormone Replacement Therapy Being Linked to Breast Cancer." *Id.* at 554-557. Wyeth's claim that the endometrial cancer story has no relevance is specious.

C. The endometrial cancer evidence is admissible for notice and Wyeth's reaction to it.

Wyeth maintains that the endometrial cancer epidemic can only be used as "prior bad acts" evidence under Fed. R. Evid. 404(b). Not true. As explained above, the first drug disaster furnished strong notice to Wyeth of the duty, as the FDA instructed, to "know its drugs." The epidemic should have taught the company to be vigilant and study potential risks that arise through signals and concerns voiced by other scientists. Wyeth had the perfect opportunity to

——————————— (Cont.)

Robbins AS, Clarke, CA, *Regional Changes in Hormone Therapy Use and Breast Cancer Incidence in California From 2001 to 2004*. J CLIN ONCOL. 2007 Jun 25; [Epub ahead of print].

[44] Ex. 35, M4546, Hulka et al., *Predominance of early endometrial cancers after long-term estrogen use*. 244(21) JAMA. 2419-22 (Nov. 28, 1980)

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avoid a second disaster but squandered it. Instead of heeding the FDA's advice and the lessons imparted by the research of Dr. Austin and other scientists, Wyeth made the strategic decision to be "vigilant in disassociating its product from cancer." *In re Prempro*, 586 F.3d at 556. Wyeth refused to conduct or sponsor breast cancer studies and attempted to stifle concerns raised by others' research. This endometrial cancer story is critical evidence of Wyeth's negligence.

D. Circumstances surrounding the endometrial cancer warning are highly relevant, not prejudicial.

Evidence is relevant if it has "any tendency to make the existence of any fact that is of consequence to the determination of the action more probable or less probable than it would be without the evidence." Fed. R. Evid. 401. The endometrial cancer evidence is undeniably relevant and thus probative. And all probative evidence is inherently prejudicial; otherwise, plaintiffs would not offer it. "Unless the judge concludes that the probative worth of the evidence is 'substantially outweighed' by one or more of the countervailing factors [under Fed. R. Evid. 403], there is no discretion to exclude; the evidence must be admitted." 22 Fed. Prac. & Proced. Evid. § 5214 (1st Ed.). Where the probative value and the potential prejudicial effect are both great, Rule 403 requires the admission of the evidence. *U.S. v. Krenzelok*, 874 F.2d 480, 482 (7th Cir. 1989). Here, the notice Wyeth received of the circumstances that led to the endometrial cancer warning in the Premarin label, and Wyeth's reaction to it, go to the heart of the issues in this case. Despite the widespread scientific support for the population trend data, as evidenced by several peer-reviewed published studies, Wyeth still maintains there is no "proof" that E+P causes breast cancer. Therefore, Wyeth claims, all of this evidence lacks probative value. No court has ever agreed with Wyeth on this point.

Wyeth abhors the endometrial cancer evidence because it is compelling. But that does not justify the exclusion of the evidence. Rule 403 gives courts the discretion of excluding probative evidence only if it is *substantially outweighed* by its prejudicial effect. The evidence is neither misleading nor confusing, nor will its presentation waste time or cause delay. Therefore,

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it should be admitted.

W6. Wyeth's Mistreatment of Animals

Plaintiffs do not oppose this motion, as long as they can explain that Premarin is derived from the urine of pregnant horses.

RESPONSES TO DEFENDANT UPJOHN'S MOTIONS *IN LIMINE*

U7. Marketing Materials that Plaintiff or Her Physicians Did Not See

The arguments defendant Upjohn makes are essentially the same as those made by its co-defendant Wyeth in Motion W1 above: Upjohn contends that its marketing materials and strategies are irrelevant unless Mary Chandler or her doctors were privy to them. However, the evidence demonstrates Upjohn's knowledge of a duty to study its drug's breast cancer risk and to avoid promoting it for unapproved uses, as well as its breach of both duties.

A. Background

Provera (medroxyprogesterone acetate, or "MPA") was approved by the FDA in 1959, but solely for treatment of secondary amenorrhea, functional uterine bleeding, infertility and related conditions. Provera was not approved for combination use with estrogen, nor was it approved for treatment of menopausal symptoms. In fact, the FDA was never approved for use every day of the month together with estrogen to treat menopause, which is how it was prescribed to Mrs. Chandler.[45] Nevertheless, Upjohn aggressively promoted Provera for daily use with Premarin throughout the 1980s and early 1990s as "the other half of hormone therapy."[46] The FDA issued warning letters to Upjohn repeatedly, rebuking the company for making these illegal marketing claims.[47]

During this same time frame, the FDA also told Upjohn there was no safety data on Provera combined with estrogen. The FDA was particularly concerned about the risk of breast

[45] In 1998, the FDA finally approved Provera, but only for cyclic therapy (10 days per month), not for continuous daily use.

[46] Ex.36, PX 10155.

[47] Ex. 37, PX10177; Ex. 38, PX 10179; Ex. 39, PX 10189.

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cancer and made clear to Upjohn that Provera would not be approved as hormone replacement therapy until it conducted proper clinical studies.[48] Meanwhile, the FDA instructed Upjohn to "remain vigilant" against marketing Provera for use with estrogen.[49] But Upjohn continued selling its drug illegally without conducting a single study on breast cancer risk.[50]

B. Upjohn's marketing activities are evidence of negligent conduct.

Throughout the 1980s and early 1990s, the FDA persistently put Upjohn on notice of the duty to study the safety of E+P and to avoid selling Provera for treatment of menopause until those studies established there was no breast cancer risk. Upjohn reacted to the FDA's notice by ignoring it. The probative value of Upjohn's marketing activities has nothing to do with whether Mary Chandler or her doctors saw these advertisements. The Eighth Circuit described the very same evidence in affirming the jury verdict in *Scroggin*, which found that Upjohn was negligent. *In re Prempro Prods. Liab. Litig.*, 586 F.3d at 560. In fact, the court summarized Upjohn's negligence under the heading "Upjohn's Reaction to Hormone Replacement Therapy Being Linked to Breast Cancer." *Id.* at 558. As in *Scroggin*, plaintiffs in this case allege negligence, not fraud or misrepresentation, against Upjohn.

U8. FDA Letters Re: Marketing Materials Plaintiff and her Physicians Did Not See

Upjohn argues for the exclusion of the FDA's admonitions to Upjohn to stop advertising Provera as "the other half" of HRT because Provera was not approved for this use and there was no scientific data to support its safety. Wyeth cites only an unpublished opinion from a single court, without mentioning that the Eighth Circuit explicitly found that this very evidence justified the jury's verdict of negligence against Upjohn. *In re Prempro Prods. Liab. Litig.*, 586 F.3d at 559-560. Furthermore, the plaintiffs in *Cross v. Wyeth*, upon which defendant exclusively relies, alleged claims of negligent misrepresentation. 2011 WL 2517211, at *4. Plaintiffs in this case

[48] Ex. 40, PX10493 at p.1.

[49] Ex. 41, PX 4969.

[50] Ex. 42, Trial testimony of Upjohn's regulatory expert, Heidi Jolson, *Scroggin v. Wyeth* at 2195:5-11; 2213:25-2214:17; 2197:5-17.

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do not. Thus, plaintiffs need not prove that Mary Chandler's doctors relied on any particular advertisement. They intend to present the FDA letters as notice to Upjohn of its duties of care and its subsequent breach of those duties.

Upjohn further maintains that the FDA communications are prejudicial and should be excluded under Fed. R. Evid. 403. But as explained above, it is clear that the evidence is highly probative of the creation and breach of Upjohn's duties to study its drug and avoid marketing it without proper safety data. Where the probative value and the potential prejudicial effect are both great, Rule 403 requires the admission of the evidence. *Krenzelok*, 874 F.2d at 482. The Court can safeguard against any potential prejudice with appropriate limiting instructions to the jury.

Finally, Upjohn contends that the FDA letters are inadmissible because they are merely "informal and advisory." In other words, because FDA didn't reduce its repeated warnings to a formal decree published in the Federal Register, there is no truth to the FDA's position. But no court has ever excluded the evidence on those grounds. Nor is it the practice of the FDA to take such measures. Rather, FDA expects drug manufacturers to heed its directives. The fact that Upjohn had to spend a significant portion of its defense responding to this evidence does not make it unfairly prejudicial. Since the FDA's warnings are critical evidence of negligence, it is not surprising that Upjohn devoted substantial time and effort at trial rebutting it. Given their strong probative value, the FDA letters should be admitted.

U9. Proposed Provera "Blister Pack"

Before 1998, Provera was approved only for treatment of abnormal bleeding, a condition that typically required a prescription for ten (10) days' use. In 1989 – knowing that it was not legally allowed to encourage or promote Provera for use with estrogen to treat menopause symptoms – Upjohn developed a 28-day blister pack for this very purpose. Upjohn also created promotional materials for physicians stating that the blister pack would make Provera easier for women to use with estrogen for HRT. Upjohn applied to the FDA to approve the blister package

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but omitted to tell the FDA that the pack would contain 28 Provera pills for each month, not the approved 10 pills per month. FDA approved the application on July 5, 1990. However, when the FDA discovered the true purpose of the blister pack, the FDA immediately halted its approval.[51] The FDA further told Upjohn, "[I]t was not our intent to approve a blister package containing this number of tablets nor to approve any package for an unapproved indication.[52]

The blister pack evidence is relevant and admissible for four reasons. First, it is probative of the FDA's notice to Upjohn that Provera was not approved for combination use with estrogen and that this regimen was not proven to be safe, particularly when used every day. Second, the evidence confirms that Upjohn was indeed promoting Provera for this untested, unapproved indication – *i.e.*, Upjohn breached its duty of care. Third, the documents rebut Upjohn's position that FDA had unlimited power to oversee drug companies. In this case, the agency lacked the clairvoyance and resources to monitor Upjohn's ongoing marketing tactics to make sure it was following both the letter and the spirit of the limitations placed on Provera's legally licensed indications. The jury should be able to decide Upjohn's liability in the face of FDA's limited oversight. And fourth, the cornerstone of Upjohn's defense at trial will be that it always complied with FDA regulations. This episode in Provera's history is important evidence of Upjohn's noncompliance with FDA regulations. If – as expected – Upjohn tells the jury that it cooperated with the FDA and complied with the agency's mandates, plaintiffs must be permitted to introduce evidence regarding the Provera blister package to rebut these claims.

U10. <u>Criminal Plea Agreements</u>

Plaintiffs have no intention of introducing evidence of Upjohn's numerous violations of Congressional law and FDA regulations to the extent they are unrelated to hormone replacement therapy. But defendants' motion is overly broad. In its efforts to convince the jury it is a "good citizen" and engages in praiseworthy activities that have no bearing on any issue of dispute,

[51] Ex. 43, PX 10180; Ex. 44, Roehl Dep. at 183-186 (Dec. 13, 2005).

[52] Ex. 45, PX 4986; Ex. 46 PX 4987.

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Upjohn will likely make such evidence relevant. For instance, if Upjohn claims it has never violated the law and has diligently followed FDA directives, such evidence is relevant for impeachment purposes. Likewise, if Upjohn boasts at trial that it makes popular drugs that are household names, or that it contributes substantial sums of money or time to charitable organizations, evidence of its criminal plea agreements becomes relevant for character impeachment. But plaintiffs assure the Court that they will first seek the Court's permission to introduce this evidence before offering it.

U11. Material Safety Data Sheet ("MSDS") Required by OSHA

Plaintiffs do not oppose this motion.

U12. Provest

Plaintiffs do not oppose this motion as it relates specifically to Provest. However, plaintiffs believe that the beagle dog studies themselves, which were mentioned in the Provera label, are relevant and admissible because they relate directly to MPA, the same molecule and active ingredient in Provera. The studies' results also put Upjohn on notice of the duty to follow up with clinical studies of women using Provera combined with Premarin for hormone replacement therapy in order to assess the risk of breast cancer.

U13. Correspondence Regarding Other HT Products (Proposed Class Labeling)

Upjohn demands the exclusion of important correspondence with the FDA on the grounds that it involved a different drug. This argument is specious. It is directly contradicted by the documents Upjohn seeks to exclude, by Upjohn's own executives and by defendant's FDA witness. Upjohn's claim that the evidence is irrelevant and prejudicial also lacks merit.

A. Background

In 2000, the FDA sent letters to several companies that marketed both estrogen replacement therapy (ERT) and combination E+P hormone therapy. The letter outlined new class warnings the FDA wanted the companies to add to their existing labels following the

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results of the Heart and Estrogen/Progestin Replacement Study (HERS).[53] Upjohn received this same letter for all of its HRT drugs. In its letter, the FDA *requested* that Upjohn and other companies make these changes "so as to furnish *adequate* information" regarding new data on breast cancer risk posed by the addition of progestins to estrogen.[54] The FDA explicitly stated, "These changes will be requested for *all* approved estrogen replacement therapy (ERT) and *estrogen/progestin combination hormonal replacement therapy*."[55]

Rather than comply with the FDA's request, Upjohn and Wyeth jointly had their legal counsel write the FDA opposing the recommendations. The letter made clear the companies' position that the FDA lacked the authority to force them to change their drug labels:

> … as a practical matter, changes in the labeling generally result from a negotiation process that recognizes and respects the different expertise and perspectives of the applicants and the agency. **It is not consistent with the law for the FDA simply to dictate proposed language for an applicant's labeling** without providing a meaningful opportunity for dialogue between the applicant and the agency.[56]

Despite the FDA's concerns about this new information regarding the association between E+P and breast cancer, Upjohn did not add a human breast cancer warning to its Provera label until 2007 – seven years later. Wyeth didn't strengthen the breast cancer warning in its Premarin and Prempro labels until 2003, after the WHI randomized trial was halted.

B. The FDA letter pertained to all HRT drugs, including Provera.

Deceptively, Upjohn claims the FDA's letter was meant to apply only to Upjohn's drug Despo-testadiol. This is not true, and Upjohn knows it. The letter itself states that the same recommended labeling change was "requested for *all* approved" HRT drug, including

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[53] *See* Defendants' Brief (Doc. No. 127) Dowse Decl. Ex. 29).

[54] *Id.* at 1, para. 2 (emphasis added).

[55] *Id.* (emphasis added)

[56] *See* Defendants' Brief at 31, Dowse Decl. Ex. 30 at p.1 (emphasis added)

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"estrogen/progestin combination hormonal replacement therapy (HRT) products."[57] Upjohn received these letters for several of its HRT drugs.[58] Wyeth got the same letter for Premarin and Prempro.[59] Upjohn's corporate executives acknowledged that the FDA wanted to apply the new warnings "across the board to all estrogen and estrogen/progestin drugs."[60] And Susan Allen, the former FDA official who authored the letters, testified at trial that the proposal was directed to *all* manufacturers of HRT drugs. "I proposed that Wyeth and every other company that made E and E plus P products include some language in their labeling, correct."[61] Further, as the Court is now well aware, E+P consists of two chemical components: estrogen and progestin. Provera is a progestin, and its primary use since the late 1970s was in combination with estrogen to treat menopause. The impetus for the FDA's recommendations to strengthen the label for HRT as a class was that the HERS study showed that the breast cancer risk is more pronounced when a progestin is added to estrogen, whether as separate pills or as a single tablet. It is simply disingenuous for Upjohn to argue otherwise.

C. The correspondence is relevant to the limitations of FDA and defendants' duties.

The FDA's letter and Upjohn and Wyeth's joint response are relevant for several reasons. First, these documents confirm what plaintiffs have always argued: the FDA has limited authority over the content of drug labels, and the manufacturer is ultimately responsible for its drug's warnings.[62] Second, the correspondence rebuts the defense Upjohn has raised at every

[57] Dowse Decl. 29 at 1.

[58] Ex. 47, PX 10424; Ex.48, PX 11201

[59] Ex.49, PX 561

[60] Ex.50, PX 11190 at 1.

[61] Ex.51, Trial Tr., Allen testimony, *Singleton v. Wyeth*, (Phila Ct. Comm. Pl., Feb. 17, 2010 a.m.) at 60:2-7.

[62] *See Wyeth v. Levine*, 129 S. Ct. 1187, 1189 (2009). "*See, e.g.*, 21 CFR § 201.80(e) (requiring a manufacturer to revise its label 'to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug'); § 314.80(b) (placing responsibility for postmarketing surveillance on the manufacturer); 73 Fed. Reg. 49605 ('Manufacturers continue to have a responsibility under Federal Law … to maintain their labeling and update the labeling with new safety information.')"

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trial, that (a) the FDA dictates every word in the label, including label changes; (b) drug companies like Upjohn are at the mercy of the FDA with respect to the contents of their labels; and (c) whatever Upjohn's label stated (including *when* it was stated) – was controlled entirely by the FDA. These two letters contradict Upjohn's "FDA defense." Outside the courtroom, Upjohn asserted the opposition situation and directly opposed the FDA by telling the agency that it may not "simply dictate" the content of the company's drug label. And third, Mary Chandler took Wyeth's Premarin (E) and Upjohn's Provera (P) from 1990 until the date of her diagnosis in 2001. The letters are undeniably relevant to the claims against both defendants.

D. The documents' relevance is not substantially outweighed by prejudice.

Given the centrality of the evidence to the issues in dispute, the mere fact that it is damaging to defendants' position is not a proper basis for exclusion. Furthermore, Upjohn's claim that the evidence may confuse or distract the jury underestimates the intelligence of American jurors. *See, e.g., Hamm v. American Home Prods. Corp.*, 888 F. Supp. 1037, 1039 (E.D. Cal. 1995) (rejecting defendants' "dark view of juror incompetence"). Appropriate limiting instructions serve to minimize concerns about potential prejudice. *Id.* Upjohn has failed to meet its burden to show that the probative value of this evidence is "substantially" outweighed by the danger of unfair prejudice.

U14. Fraud on the FDA

Plaintiffs do not oppose this motion. However, plaintiffs note that the authorities cited by defendant do not hold that allegations of violations of FDA regulations are barred under the preemption doctrine. Nor do these cases preclude plaintiffs from presenting evidence that defendants defied or ignored FDA's recommendations or directives.

PLAINTIFFS' RESPONSE TO DEFENDANTS' MOTIONS *IN LIMINE*

D.15 Warnings and Labeling Changes that Post-Date Plaintiff's HT Use

Defendants' chief argument is that the label changes that post-date Mrs. Chandler's use of E+P are "subsequent remedial measures," which are not admissible to prove negligence. But

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plaintiffs do not offer this evidence to show negligence. Rather, they offer it for other distinct purposes that have nothing to do with culpability. In their motion, defendants fail to acknowledge this.

Fed. R. Evid. 407 "does not require the exclusion of evidence of subsequent measures when offered for another purpose, *such as* proving ownership, control, or feasibility of precautionary measures, if controverted, or impeachment." (emphasis added). Here, plaintiffs offer subsequent changes to defendants' E+P labels for three key purposes: causation, feasibility, and impeachment. In addition, label changes at the behest of the government are not subsequent remedial measures. Several courts in the HRT litigation have denied defendants' similar motions and admitted the evidence – a fact defendants overlook. Furthermore, defendants' claim that the evidence is unfairly prejudicial is implausible. In every trial, defendants introduce their own subsequent actions. Thus, it is plaintiffs who would be prejudiced by the exclusion of the label changes.

A. <u>The evidence is relevant to prove general causation and the feasibility of ascertaining the true breast cancer risks earlier.</u>

At the heart of plaintiffs' case is their contention that defendants avoided studying the breast cancer risk of E+P despite countless red flags that raised suspicion of the risk, and they failed to warn – indeed, hid – the risk of breast cancer even when it became evident in the literature. As a result, defendants kept the medical community in the dark about that risk, thereby preventing an adequate warning to patients like Mrs. Chandler.

Here, causation is distinct from negligence. As the Fifth Circuit has long recognized, "[S]ubsequent remedial measures can be introduced on the issue of causation if that is in controversy." *Brazos Rivers Auth. V. GE Ionics, Inc.*, 469 F.3d 416, 429 (5th Cir. 2006). A decision from the Northern District of Illinois explains, "Because causation is analytically distinct from fault ('negligence or culpable conduct'), it is plainly 'another purpose' for which evidence of subsequent remedial measures can be offered under Rule 407." *Weatherill v. Univ.*

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of Chicago, 565 F. Supp. 1553, 1558 (N.D. Ill. 1983). To this day, defendants maintain that there is insufficient evidence of general causation. The current labels contradict this claim.

None of the cases cited by defendants involved the use of post-incident labels to establish proximate cause or general causation.[63] And defendants' claim that comment k mandates that their labels be judged by the science of the time ignores the scope of knowledge to which manufacturers are held under Washington law. *See Lockwood v. AC&S, Inc.*, 1209 Wash. 2d 235, 269, 744 P.2d 605, 624 (Wash. 1987) ("In determining the scope of a manufacturer's duty to warn of dangers associated with its products, a manufacturer is under a duty to test, analyze and inspect such products, and is charged with knowing what such tests would have revealed.").

Nevertheless, defendants' argument is beside the point – plaintiffs offer the current labels not to prove misconduct, but to prove causation, a fact defendants hotly dispute. The current label admits breast cancer is a known side effect caused by E+P. This admission flatly contradicts Wyeth's claim that causation is not established. Although defendants claim they do not contest the feasibility of a stronger warning at the time Mrs. Chandler took E+P, they ignore two of their cornerstone defenses in this litigation: (1) that the FDA would not have permitted a stronger warning before the WHI results were released; and (2) that they could not have conducted any studies to assess accurately the risk of breast cancer any earlier than when the WHI was conducted. Defendants' arguments directly contest the feasibility of any earlier warnings.

As plaintiffs point out in their response to U13 above, defendants could have strengthened their label, as recommended by the FDA, to warn of a heightened risk of breast cancer from the HERS study. It was also feasible for defendants to conduct their own case-control studies on breast cancer risk, as urged by the FDA as a condition to the approval of

[63] *See, e.g., Werner v. Upjohn Co.,* 628 F.2d 848, 853-54 (4th Cir. 1980) (new label introduced solely to establish negligence); *Stahl v. Novartis Pharms. Corp.*, 283 F.3d 254, 270-71 n. 10 (5th Cir. 2002) (plaintiff admitted he sought to introduce post-use label to prove prior label inadequate).

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Prempro.[64] And Wyeth was aware from the previous uterine cancer epidemic it incited that case-control studies were the appropriate design for measuring cancer risk. *See* response to W5 above.

Directly on point is a decision by the federal district court in *McAdams v. Eli Lilly & Co.*, No. 77-C-4174, 1981 U.S. Dist. LEXIS 18187 (N.D. Ill. Oct. 6, 1981).[65] There, the defendant filed a motion *in limine* to prohibit post-use documents asserting, as defendants do here, that the science of the time did not support a different warning. The court found that the feasibility exception to Rule 407 applied. The court also noted "the subtle manner in which a defendant may controvert feasibility" by claiming the lack of sufficient information at the time to issue warnings. *Id.* at *5. As the court pointed out, "Feasibility also embraces the factual basis upon which the change could be made." *Id.* at *6.

Because Wyeth hotly disputes general causation as well as the feasibility of adequately warning sooner – particularly the factual basis upon which the warning could be made – the evidence is admissible for these purposes.

B. The evidence is relevant to prove proximate causation.

To prove *culpability,* plaintiffs will show that defendants failed to act as reasonably prudent manufacturers in failing to do the studies that would have revealed known or knowable risks. But to prove *proximate cause,* plaintiffs will prove that a better subsequent warning would have made a difference to Mrs. Chandler and her doctors. Mrs. Chandler testified that she felt her doctors would never have prescribed E+P to her if it was dangerous and could cause breast cancer.[66] She would not have taken E+P or would have quit taking it had she known that it carried a significant risk of breast cancer. Second Amended. Complaint, Doc. No. 47 at ¶ 17.

Dr. Velcoff was the physician who first prescribed E+P to Mrs. Chandler. She testified

[64] Ex. 52, PX 287 Prempro Approval Letter (Dec. 30, 1994)

[65] Attached as Ex. 53.

[66] Ex. 54, Mary Chandler Dep. at 153:10-154:2 (April 1, 2009).

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that she was not aware that there was a risk of breast cancer with E+P, otherwise she wouldn't have even taken it herself. Dr. Velcoff relied on the PDR (physicians' desk reference), which is a compilation of drug labels, as a primary resource.[67] Dr. Velcoff assumed that E+P was cardio protective and prevented osteoporosis, and the only risks were blood clots and phlebitis.[68] Mrs. Chandler's other prescribers at Kaiser relied on Kaiser's internal guidelines.[69] Dr. Galitz understood that the risk of breast cancer from E+P was very low, especially compared to significant benefits of E+P in preventing hip fracture and cardiovascular disease.[70] It is no longer the practice of family practitioners at Kaiser to prescribe HRT.[71] Cathie Gurgel, plaintiff's nurse practitioner, testified that she and her colleagues no longer prescribe E+P for treatment of menopausal symptoms, based on information from the WHI.[72] Previously, the collective belief was that E+P was good for breast health, the brain, the heart, "all sorts of things."[73] Ms. Gurgel relied on the PDR for information on drugs and their side effects.[74] According to Ms. Gurgel, the current label provides more specific information than she had before.[75]

C. The evidence is admissible for impeachment purposes.

The current E+P labels impeach the claims defendants make at every trial that E+P does not cause breast cancer in *anyone*. For example, defendants' own experts define a "side effect" as something that is expected to happen in a certain percentage of women taking the drug,"[76] or

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[67] Ex.09, Velcoff Dep. at 69:6-11 (Aug. 17, 2009).

[68] *Id.* at 31:17-32:2.

[69] Ex. 55, Galitz Dep. at 27:7-13 (Apr. 8, 2011).

[70] *Id.* at 20:21-21:18; 23:22-25:8.

[71] *Id.* at 45.

[72] Ex. 10, Gurgel Dep. at 54:21-55:10.

[73] *Id.* at 49:3-12.

[74] *Id.* at 60:14-61:6.

[75] *Id.* at 69:6-15.

[76] Ex. 56, Trial testimony of Dr. Shawna Willey, Wyeth's oncology expert, *Henry/Buxton v. Wyeth* at 36 (Aug. 5, 2010 p.m.).

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"a bad thing that happens as a result of taking the drug," [77] "a certain percentage will get this effect from taking the drug,"[78] or "an effect that we now that the drug causes and it causes it in a regular manner."[79] Yet at trial, Wyeth tells the jury there is no evidence that E+P cause breast cancer generally or has any effect on its development. This position is sharply contradicted by the exact language that Wyeth and Pfizer put in their current labels.

D. The evidence is admissible to rebut Wyeth's argument that FDA still finds E+P safe and effective.

Wyeth argues throughout every trial that E+P remains on the market in the U.S. and continues to enjoy approval of the FDA. Wyeth will argue that this confirms that the FDA still considers E+P "safe and effective" and doctors still prescribe it women today.[80] Under the circumstances, plaintiffs should be entitled to show the jury the current label, which clearly states that E+P increases the risk of invasive breast cancer, that the risk goes up with every year of use, and that breast cancer is now a recognized side effect of the drug.[81] For this very reason, the court in *Kendall v. Wyeth* rejected defendants' post-trial argument that this evidence should not have been admitted.[82]

The evidence is admissible because the black box warning is mandated by FDA.

Courts consistently hold that remedial actions compelled by third parties are not subsequent remedial measures. *Pau v. Yosemite Park and Curry Co.*, 928 F.2d 880, 888 (9th Cir.

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[77] Ex. 57, Trial testimony of Dr. Geza Acs, Wyeth's pathology expert, *Henry/Buxton v. Wyeth*, at 78-79 (Aug. 11, 2010).

[78] Ex. 58, Trial testimony of Dr. Elizabeth Morris, Wyeth's radiology expert, *Henry/Buxton v. Wyeth*, at 77-78 (Aug. 16, 2010).

[79] Ex. 57, Acs testimony at 78-79, *Henry,Buxton* (Aug. 11, 2010).

[80] *See, e.g.*, Ex. 59, Trial Tr., *Scroggin v. Wyeth* at 134:1-9 (opening statement); Ex. 60, Tr., *Nelson v. Wyeth* at 92-93 (opening statement, Jan. 11, 2007); Ex. 61, Tr., *Barton v. Wyeth* at 67:12-19 (opening statement, Sept. 16, 2009).

[81] Ex. 62 PX M5399 2010 Prempro Label at 17 (serious but less common side effects of E+P: breast cancer).

[82] Ex. 63, Opinion on Post-Trial Motions, *Kendall v. Wyeth & Upjohn*, No. 00965 (Phila. Ct. Comm. Pl. June Term 2004) (Mar. 18, 2010) at 14.

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1991). *See also Millenium Partners, L.P. v. Colmar Storage, LLC*, 494 F.3d 1293, 1303 (11th Cir. 2007) (joining seven other Circuits that have held Rule 407 does not apply to remedial measures by a non-party). This exception is particularly strong when the third party is the government, as here. Actions taken pursuant to government mandates are not subsequent remedial measures entitled to protection from disclosure because the manufacturer must comply with government requirements. *See In re Aircrash in Bali, Indonesia*, 871 F.2d 812, 816-17 (9th Cir. 1989) (safety report that post-dated air crash did not qualify as a subsequent remedial measure because it was prepared by the FAA and defendant was legally obligated to cooperate with the FAA's investigation).

This is also true when the FDA is the agency involved. FDA regulations mandate that a drug company change its labels as soon as it becomes aware of a substantial risk. 21 CFR § 201.80(e). But only the FDA can order a "black box" warning like the one it required for breast cancer after WHI. Defendants concede this. Defendants also concede that the FDA implemented class labeling that defendants were obliged to adopt after the WHI. The court in *Barton v. Wyeth* likewise found that exclusion of the current label runs counter to the purpose of Rule 407.[83]

The probative value is not substantially outweighed by prejudice.

As explained above, defendants will elicit their own evidence post-dating Mrs. Chandler's surgery by arguing that their drugs are still on the market, that the FDA endorses their safety, that E+P is the best treatment for menopause, to this day there is no scientific evidence that E+P causes breast cancer, and there is no way defendants could have done studies to measure this risk. If plaintiffs are precluded from rebutting these claims, it is *they* – not defendants – who will suffer irreparable prejudice.

D16. Causality Assessments Performed in the Regulatory Context

Defendants exhaustively argue for the exclusion of this evidence for two reasons –

[83] Ex. 64, Order, Post-Trial Motions, *Barton v. Wyeth* at 45 (Jan. 29, 2010).

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neither of which has any relevance. Specifically, defendants claim that plaintiffs and their experts rely on causality assessments to prove general causation and to prove specific causation. But in fact, plaintiffs do not intend to use Wyeth's causality assessments for these purposes. The point of the evidence is twofold: (1) to impeach *defendants'* experts who opine that there is no reliable methodology for assessing causation; and (2) to prove that the causality assessments put Wyeth on notice of the need to follow up with proper studies on breast cancer and warn about the risks such studies would have revealed. Other courts in the HRT litigation have admitted the causality assessments for these very reasons. Because defendants' arguments rest on an invalid premise, the cases they cite do not aid their position.

Wyeth has a written protocol for assessing causation of adverse events associated with its E+P drugs. Assessing whether a causal connection exists between an adverse drug reaction associated with the use of a drug is a typical safety function in the post market monitoring of any medication and is essential in the exercise of pharmacovigilance. Wyeth did such assessments in its clinical trials when women participating in them developed breast cancer. In each case, one of Wyeth's safety doctors would review the woman's entire medical history and issue an opinion on whether E+P was causally related. A second doctor would review the assessment, then both doctors made a final causation assessment.

A. The evidence is admissible for purposes of impeachment.

Wyeth's experts' reports all read the same way. They claim that it is impossible to determine the cause of breast cancer in any individual woman, and causality assessments have no place in their practices. Dr. Barbara Levy's opinions are no different: "Scientists recognize that breast cancer has many potential causes or influences, most of which are unknown at this time. Therefore, any attempt to assign causality based on currently recognized risk factors is scientifically unjustified… I have never used a differential diagnosis process or a "causality assessment" to attempt to identify the cause of a patient's breast cancer or any other cancer and I

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do not know of any practicing physician who has." [84]

Evidence that Wyeth's own physicians conducted causality assessments in its clinical trials is therefore relevant for impeachment purposes. So is the testimony of Wyeth's own scientist, Songlin Xue, who explained that the causality assessment process is similar to how he would diagnose his own patients in a clinical setting: "Just like a patient walks to a doctor's office and presents with a headache. The doctor asks a whole bunch of questions very similar to this to try to sort out what really caused the headache."[85]

Plaintiffs neither use nor need to use causality assessments to establish causation. There are now more than 44 published epidemiological studies that confirm general causation and show greater than a doubling of the risk for breast cancer in women using E+P.[86] There are also population studies showing a dramatic and unprecedented drop in the breast cancer rate in this country that directly matches the corresponding drop in E+P use.[87] So commonly accepted is the biological evidence linking E+P and breast cancer that it is now stated in medical textbooks and generally recognized in the medical community.

While plaintiffs' experts use the same basic methodology as Wyeth's safety physicians did when conducting causality assessments of breast cancer in clinical study participants, these experts do not rely on Wyeth's particular assessments to establish causation, or in lieu of their own causation analysis. The court can give the jury a limiting instruction to this effect.

B. The evidence is admissible for notice of the need for further studies and warnings.

Critical to plaintiffs' theory that defendants failed to study the relationship between E+P and breast cancer is evidence of "red flags" or safety signals that put defendants on notice of their duty to study this risk. One of the "red flags" is the causality assessments from Wyeth's

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[84] Ex. 65 Levy Report at 5 (May 4, 2011).

[85] Ex. 66, Xue Dep. at 74-76

[86] Ex. 67

[87] Ex. 68, M5358 Marshal, *Recent Breast Cancer Incidence Trends According to Hormone Therapy use: The California Teacher's Study Cohort,* BREAST CANCER RES. (2010) at 12.

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own clinical trials, which identified a "possible," "probable," or "definite" relationship between participants' breast cancers and E+P use. When Wyeth conducted one- and two-year studies looking for benefits of E+P, it found that some women developed breast cancer, possibly due to the drug.[88] Yet Wyeth never warned doctors that E+P might cause breast cancer in as little as one to two years. The same data so troubled the FDA that it told Wyeth that in exchange for conditional approval of Prempro, it must conduct case-control studies to measure the breast cancer risk attributable to E+P.[89] Wyeth admitted it never included that information in its Prempro label or followed up with any additional studies.[90]

C. The evidence has been held admissible in other HRT trials.

Defendants fail to mention that several trial courts in the HRT litigation have permitted plaintiffs to introduce evidence of Wyeth's E+P causality assessments, and for the same purposes for which plaintiffs in this case offer them.[91] Instead, defendants cite case law that has no application to this case. For example, defendants rely on an unpublished federal opinion in the Accutane litigation. Def. Br. at 37. But in that case, the issue was whether causality assessments could be used as evidence of general medical causation *in the absence of* published science on the issue. Unlike the plaintiff in *Accutane,* plaintiffs here do not offer the causality assessments to prove causation. They offer them to prove defendants' duty to follow up on the assessments with further studies, and to show that the process of deductive reasoning, causality assessments or differential diagnosis, is not merely a litigation construct of plaintiffs' experts, as defendants

[88] Ex. 69, PX00285 at p. 22 (Patient # 30155-019).

[89] Ex. 70, PX 00288, FDA Medical Officer Review at 74 (Dec. 30, 1994)

[90] Ex. 71, Justin Victoria testimony, Trial Tr., *Scroggin v. Wyeth* (Feb. 7, 2008) at 694:10-696:11.

[91] Ex. 71, *Scroggin v. Wyeth* (E.D. Ark. Feb. 7, 2008) at 694;10-696:11; Ex. 72, *Reeves v.Wyeth*, (E.D. Ark. Aug. 25, 2006) at 788:1-789:10; Ex. 73, *Rowatt v. Wyeth*, Vol. XVIII (Nevada, Oct. 4, 2007) at 4570:10-4573:14; Ex. 74, *Daniel v. Wyeth*, (Phila. Ct. Comm. Pl. Jan. 22, 2007 p.m.) at 39:25-45:12; Ex. 75, Trial Tr. Beginning at 70, *Barton v. Wyeth*, (Phila. Sept. 29, 2009 a.m.)(entirety of testimony not included); Ex. 76, *Kendall v. Wyeth*, (Phila. Nov. 4, 2009 p.m.) at 40:16-42:7; Ex. 77, *Singleton v. Wyeth*, (Phila. Feb. 9, 2010) at 84:6-86:16; Ex. 78, *Henry/Buxton v. Wyeth*, (Phila. Aug. 3, 2010 p.m.) at 85:4-92:19 and (Aug. 4, 2010 a.m.) at 52:13-59:7. The MDL court did not admit the evidence in the trial *Wilson v. Wyeth* last year.

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and their experts contend.

The published opinion of *In re Accutane Prods. Liab. Litig.*, 511 F. Supp. 2d 1288, 1297 (M.D. Fla. 2007) better explains the distinction between the causality assessments in *Accutane* and Wyeth's assessments in its E+P trials. First, the *Accutane* assessments were based on adverse events that were received randomly by outside reporters. They were not limited to the clinical trial participants and there were no complete medical files for each patient. In addition, the methodology got watered down in time, so the evaluation was limited to a "yes/no" question based on the opinions of outside reporters. Thus, there was no way to independently review these decisions. In contrast, Wyeth's evaluations followed a protocol that did not suffer from these hindrances.[92]

Defendants also rely on *Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434 (W.D. Pa. 2003). That case is inapposite. First, the expert in *Soldo* replied on causality assessments to prove causation. Second, the expert was not aware of the methodology used by the company to perform the assessments because it was not adequately described anywhere. *Id.* at 464. Here, Wyeth has written protocols used by its safety physicians and investigators. Third, the *Soldo* assessments were not performed by the defendant drug company. *Id.* Fourth, the plaintiff's injury in *Soldo* was not the injury that the causality assessment addressed. And fifth, the *Soldo* court was concerned that the company's methodology was not generally accepted in the scientific community. *Id.* at 465. Here, Wyeth's manual is based on protocols and procedures required by the FDA for evaluating adverse events, including cancer.[93]

Similarly, defendants' reliance on cases such as *Glastetter v. Novartis Pharms. Corp.*, 107 F. Supp. 2d 1015 (E.D. Mo. 2000) are not helpful. *Glastetter* simply reflects the court's disfavor of single causality assessments, like single case reports, to prove causation. Again, plaintiffs do not offer this evidence for causation purposes, and the court can instruct the jury

[92] *See* Ex. 79, PX01680 at 8-9.

[93] Ex. 80, PX08031 at 8.

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that the reports are not probative of causation.

D. The evidence is not unfairly prejudicial.

Defendants want to exclude this evidence because it prevents them from telling jurors that medical science has never heard of a way to assess on a more-likely-than-not basis of whether a causal relationship exists between E+P and cancer. Yet Wyeth embarked on precisely this endeavor, and in the same manner as plaintiffs' experts, with more than 50 individual women in its own clinical trials. The evidence is certainly relevant to impeach Wyeth's experts and to show that Wyeth ignored safety signals from its own studies. The fact that the evidence is effective is not a valid basis to exclude it on the basis of prejudice.

D17, D22 Sales Trends and the Number of Women Whose Breast Cancer Was Purportedly Caused by HT

Defendants seek to exclude two related categories of evidence – sales trends and the scientific evidence of the number of excess breast cancers attributable to E+P. In the past, defendants have filed one motion to exclude both types of evidence. Here, defendants file them separately, presumably to distract the Court from seeing that these categories of evidence are really two sides of the same coin. It is also a belated, back-door attempt to exclude scientific evidence, which – tellingly – defendants did not oppose in their *Daubert* motions. This tactic prevents plaintiffs from responding in full detail with an explanation of the numerous studies supporting their experts' opinions and their underlying methodology.

The absolute risk of breast cancer, as expressed in the numbers of cancers caused by E+P, has been published in the peer-reviewed literature, and the methodology for calculating these numbers is generally accepted in the epidemiological and public health communities. The sales trend data, which have also been published in several peer-reviewed studies, demonstrates that following the halt of the WHI study, the number of E+P prescriptions fell dramatically. At the same time, hormone-receptor positive (ER+) breast cancers among women in the menopausal age group fell at a corresponding rate. Researchers widely attribute this trend to E+P use.

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Leading scientists have considered this evidence to be powerful evidence that E+P causes breast cancer and does so by a promoter effect. Plaintiffs will introduce this evidence at trial for three main purposes: (1) to prove general causation; (2) to prove that defendants were negligent because they had notice of a similar cancer promotion effect with the "E" component of their HRT drugs; and (3) to rebut defendants' repeated arguments that the absolute risk of breast cancer is *de minimus.*

Because the evidence of absolute risk and sales trend epidemiology is so compelling, defendants have fought with increasing vigor to keep it from the jury. But defendants' argument is hypocritical. Their message to the jury *in every single previous trial* has been that millions of women benefit from E+P. They claim that E+P is the most effective treatment for menopausal symptoms, and the absolute risk of breast cancer, as expressed in numbers of women from the WHI trial who developed it, is miniscule compared to the number of women who benefit from the drug. But when plaintiffs seek to put defendants' story in perspective by showing that this supposed benefit came at a cost of 200,000 preventable breast cancers, defendants scream "foul," claiming it is prejudicial for any party other than defendants to frame the breast cancer risk in terms of absolute numbers and percentages.

This double-standard is not only unscientific; it is unfairly prejudicial to plaintiffs. Defendants should not be entitled to cherry pick the statistical evidence that favors their litigation theory, while barring plaintiffs from plaintiffs' experts from relying on peer-reviewed, population-based epidemiological data to support their opinions that E+P causes breast cancer.

A. Other courts have denied defendants' similar motions and held that the methodology for calculating excess breast cancers caused by E+P is reliable and admissible.

While defendants point to isolated decisions from Florida excluding this evidence, they fail to mention that overwhelmingly, other courts have denied similar motions, including the

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MDL judge, six judges in Pennsylvania, two judges in Nevada and a judge in New Jersey.[94] In the past, defendants have challenged the reliability of the experts' calculations of the number of excess breast cancers caused by E+P and have demanded *Daubert* or *Frye* hearings on the issue. In New Jersey, the court conducted a full hearing on the admissibility of Dr. Graham Colditz's testimony concerning excess breast cancers and found that the methodology he employed was generally accepted. "Dr. Colditz's opinion about excess breast cancers related to combination hormone therapy is reliable and based on a standard method used by epidemiologists… Contesting the numbers that Dr. Colditz chose to use in his equations is more appropriate for cross-examination during trial."[95]

Since that hearing, Dr. Colditz's statistical analysis and conclusions were published in a peer-reviewed journal. The study confirmed that the decline in the use of E+P after the WHI study resulted in "approximately 10,000 fewer cases" of breast cancer each year.[96] Defendants have strategically chosen not to file any challenges to plaintiffs' experts' methodology for calculating excess breast cancers caused by E+P. Instead, they now use motions *in limine* as their maneuver for seeking exclusion of the evidence, long after the deadline for filing *Daubert* motions. They hope to convince courts to exclude this convincing scientific evidence on the grounds that it is prejudicial.

B. The evidence is relevant and admissible to prove general causation.

Like Dr. Colditz's paper on the number of breast cancers attributable to E+P, analyses of breast cancer and sales trends (also called "population based studies," "trend data" or "ecological" studies) provide strong epidemiological evidence of causation. These studies compare the number of E+P prescriptions sold (to determine how many women took E+P) with

[94] Ex. 81, Trial Tr., *Reeves v. Wyeth* (Aug. 23, 2006) at 432:16-433:1; Ex. 82, Trial Tr., *Rush v. Wyeth* (Feb. 8, 2007) at 2367:7-2368:10; Ex. 83, Order, *Scroggin v. Wyeth*, Case No. 04-1169, Doc. No. 602 (E.D. Ark. Mar. 3, 2008) (admitted in punitive damages phase); Ex. 84, Orders admitting the evidence in other cases.

[95] Ex. 85, Order, *Deutsch v. Wyeth* (Jun. 19, 2007).

[96] Ex. 86, MA4681, Colditz 2007.

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the number of women who developed hormone-dependent breast cancers (incidence rates). In its discussion of determining whether an exposure is a cause of disease, the REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, 2D ED. (Federal Judicial Center) endorses ecological studies: "… But when such data are available and eliminating exposure reduces the incidence of disease, this factor strongly supports a causal relationship." *Id.* at p. 378.

Establishing causation in a medical products liability case is a two-step process, requiring plaintiffs to establish both general and specific causation. Defendants, of course, dispute the evidence of causation. But given their widespread general acceptance in the scientific community (with the exception of defendants' experts), these studies are part of a reliable foundation for plaintiffs' experts' general causation opinions. Unless defendants concede causation – which they decidedly have not – Mrs. Chandler must satisfy her burden to prove this first step through epidemiological and other studies. The ecological studies have consistently found that on a population basis, the incidence of ER+ breast cancers declined when sales of E+P declined.[97] In one of the papers from the WHI, the lead investigator stated that this decrease in breast cancer in the population after the use of HRT "decreased substantially" in the U.S. "suggested a cause and effect relation."[98] There is broad general acceptance of this conclusion. The American Cancer society recently recognized that this dramatic drop in cancer rates was due to a corresponding decrease in E+P sales.[99]

The trend data also provides a plausible mechanism for causation. Dr. Ravdin's paper explains the value of this evidence. "The most plausible explanation is that stopping menopausal hormone therapy removes the fuel that is promoting the growth of some tumors."[100]

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[97] *See* Ex. 32, M4743, Ravdin et al. 356 N ENG J MED 16 (2007); Ex. 87, M4771, Clarke and Glaser, CANCER CAUSES CONTROL (2007), Ex. 88, MA4672, Kerlikowske, 99(17) JNCI (2007); Ex. 34, M4770, Robbins and Clarke, 25(23) J Clin Oncol (Aug. 10, 2007); Ex. 89, M4774, Glass, 99(15) JNCI (2007); Ex. 33, M4586, Clarke, Letter to Editor, in 24(33) JCNI (2006).

[98] Ex. 90, M4881, Chlebowski 360:6 NEJM 573, 573 (Feb. 5, 2009).

[99] Ex. 91, PX 8728, ACS' Facts & Figures, at 4 (2007)

[100] Ex. 92, M4775, Berry and Ravdin, 99(15) JCNI 1139, 1140 (2007).

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C. The evidence is relevant to plaintiffs' negligence claims.

The promoter effect observed by Dr. Ravdin and others should not be a surprise to defendants. As described above in response to Motion W5, Dr. Austin's similar ecological studies showed that prescriptions of E fell rapidly in response to news about studies linking E and endometrial cancer, a result he and his colleagues attributed to the drug's promoter effect. Wyeth and Upjohn should have heeded lessons learned from the endometrial cancer epidemic. Had they monitored breast cancer trends among menopause aged women by analyzing readily available data from cancer registries, they would have quickly seen an increase in ER+ breast cancer in that demographic population of E+P users. They knew that epidemiological case control studies were the best and quickest way of confirming whether the increase in breast cancer was causally related to E+P, but they made the conscious choice to avoid doing such studies. A jury is entitled to consider the scientific parallels between both cancer epidemics in assessing defendants' liability.

D. The evidence is relevant and necessary to rebut defendants' claims that the absolute risk of breast cancer from E+P was small.

Defendants will defend their old E+P labels by focusing on what they call the "low absolute breast cancer risk of E+P. Defendants will even insist that the WHI randomized clinical study, which was published in July 2002, actually demonstrated a lower absolute risk than what Wyeth had already been reporting to physicians. Wyeth will show the jury graphics to argue that E+P "causes only three excess breast cancers per 1,000 women." Wyeth will also contend that the difference between women in the study who used E+P versus women who did not was a "difference of less than one-tenth of a percent in the risk."[101] Plaintiffs' evidence of the actual number of excess breast cancers and the corresponding ecological data will help show why this is a distortion of Wyeth's pre-WHI label and a mischaracterization of the science.

E. The evidence is not unfairly prejudicial to defendants.

[101] *See, e.g.*, Ex. 93, Opening Statement, *Kendall v. Wyeth* at 36:16-37:12 (Oct. 20, 2009 p.m.)

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Statistical evidence of the risk of E+P and breast cancer is central to the issues in this case. Both plaintiffs' and defendants' experts have expressed their opinions on both the relative risk and absolute risk of breast cancer from E+P. The jury will be asked to weigh this hotly contested issue of causation. There is no doubt that the evidence of excess breast cancers and sales trend data is unfavorable to defendants' positions, as is the growing volume of epidemiological data confirming the association between E+P and breast cancer. But plaintiffs have the burden to prove that defendants' drugs can cause breast cancer and did cause it in Mrs. Chandler. Thus, plaintiffs must be permitted to use this scientifically reliable evidence to meet their burden. Wyeth's motion is simply a protestation of the obvious: plaintiffs' evidence is not only accurate and reliable, but effective and persuasive. This is not a proper basis for exclusion. Where the probative value and the potential prejudicial effect are both great, Rule 403 requires the admission of the evidence. *Krenzelok*, 874 F.2d at 482. Under these circumstances, careful limiting instructions to the jury are the appropriate way of minimizing potential prejudice.

D18. Evidence and Argument that Defendants Failed to Test

This motion boils down to defendants' dislike for plaintiffs' theory of the case. Defendants suggest there is no legal factual basis for plaintiffs' theory. *Au contraire*, the facts speak for themselves: defendants' failure to heed the notice they repeatedly received from the FDA and other sources of the need to do proper studies on E+P and breast cancer led to a failure to warn. Moreover, Washington recognizes the legal validity of plaintiffs' theory of liability. *See Lockwood v. AC&S, Inc.*, 1209 Wash. 2d at 269, 744 P.2d at 624 (Wash. 1987) ("In determining the scope of a manufacturer's duty to warn of dangers associated with its products, a manufacturer is under a duty to test, analyze and inspect such products, and is charged with knowing what such tests would have revealed.").

As defendants know, the failure to conduct adequate studies, which led to inadequate warnings, has consistently been plaintiffs' trial theme. Defendants can no more dictate how plaintiffs try their case than plaintiffs can decide how defendants try theirs. Furthermore,

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defendants' boilerplate recitation of prejudice is both unintelligible and meaningless. Defendants cannot even articulate why the theory plaintiffs have pursued is prejudicial, other than to imply that going to trial will make them look like "bad companies." Defendants have simply made no showing that evidence of their failure to study their drugs' potential dangers is unfairly prejudicial.

D19. References to Pfizer

Even if defendants were to prevail on their summary judgment motion, they cannot expect to hide their identity from the jury. The truth is, Pfizer acquired Wyeth. Wyeth is the company that made Premarin (E). Wyeth no longer exists as a separate, operating business. It was subsumed into Pfizer, Inc. Pfizer also acquired Upjohn and Pharmacia, the companies that made Provera (P), the progestin Mary Chandler took in combination with Premarin. Upjohn and Pharmacia no longer exist as separate business entities. They, too, were subsumed into Pfizer, Inc. The jury should at least be told that the lawyers defending these drugs now work on behalf of Pfizer. Here, too, defendants have made no showing that disclosing the identity of Pfizer is unfairly prejudicial.

D20. 2006 GAO Report

Defendants misstate the purpose for which plaintiffs offer the GAO report. They also ignore its relevance and fail to mention that it has been admitted for this limited purpose in numerous HRT trials.

In 2006, the GAO issued a report on the FDA's post-approval oversight of prescription drugs over the previous decade. The report found that the FDA lacked the power to enforce companies to comply with their commitment to conduct post-marketing ("Phase 4") studies to assess their risks in exchange for granting the drugs' approval. This lack of authority, in turn, hampered the FDA's ability to protect public health and safety because the companies had no incentive to perform safety studies once their drugs were widely sold to the public. As it turned out, Baycol, Propulsid and other drugs caused many injuries and death, which could have been

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prevented had the FDA been able to compel the companies to do safety studies right away. While the report focused on drugs other than E+P, the same regulations (and limitations) applied to *all* prescription drugs, as is clear from the report's conclusions:

> [The] FDA had limited authority to require that sponsors conduct postmarket safety studies…[102]
>
> ***
>
> Data constraints – such as weaknesses in data sources and limitations in requiring certain studies and obtaining data – contribute to FDA's difficulty in making postmarket drug safety decisions … The availability of these data sources is constrained, however, because of FDA's limited authority to require drug sponsors to conduct postmarket studies and its resources.[103]

Hence the importance of this evidence: the GAO report explains why the FDA could not force Wyeth to make good on its commitment to conduct case-control studies on breast cancer in exchange for approving Prempro. After the GAO report was published, Congress amended the Food Drug & Cosmetic Act to give the FDA the power to enforce these postmarketing commitments. But at the time Mrs. Chandler took E+P, the FDA had no such authority. Plaintiffs' regulatory experts rely on the GAO in part for their opinion that the FDA's power at the time was far from limitless, particularly in its oversight of E+P.

The GAO report is also relevant because in previous trials, defendants and their experts have maintained that "FDA has regulatory authority over Premarin and Prempro and can take enforcement action against either drug if warranted."[104] Defendants also claim that they complied fully with the FDA at every step, and that the FDA would not have allowed "continued marketing of Premarin or Prempro unless the drugs' labeling complied with FDA

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[102] *See* GAO Report at 11 (Dowse Decl. Ex. 64)

[103] *Id*. at 24.

[104] Ex. 94, Susan Allen Expert Report at 18 (Mar. 20, 2007).

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regulations."[105] For this very reason, the MDL court, among others, admitted the GAO report into evidence to rebut defendants' position on the expansive role of the FDA in drug oversight.[106]

Courts in other litigations have rejected the identical arguments defendants make, holding that the 2006 GAO report is admissible as evidence of the FDA's limited resources. *See, e.g., Bartlett v. Mutual Pharmaceutical Co., Inc.*,759 F. Supp. 2d 171, 188 n. 16 (D.N.H. Jan. 5, 2011) (rejecting defendant's renewed motion for judgment as a matter of law and noting that the 2006 GAO Report, along with another government report were a reliable basis for plaintiff's experts' testimony concerning the limitations of FDA resources).

The evidence is plainly relevant and should be admitted. Rule 403 warrants exclusion of relevant evidence only if its probative value is *substantially outweighed* by the danger of unfair prejudice. "Consistent with the requirement that the overbalance must be substantial, we have said: 'In weighing the probative value of evidence against the dangers and considerations enumerated in Rule 403, the general rule is that the balance should be struck in favor of admission.'" *Block v. R.H. Macy & Co., Inc.*, 712 F.2d 1241, 1244 (8th Cir. 1983) (internal citations omitted). Defendants' fear of potential jury confusion is exaggerated, and it underestimates the jury's ability to consider the evidence – particularly when given a limiting instruction by the Court. *Hamm*, 888 F. Supp. at 1039.

D21. <u>Defendants' Wealth, Profit Margins for HT and "Profit Motive"</u>

Plaintiffs have already agreed not to introduce evidence of defendants' net worth or ability to pay a verdict because punitive damages are not at issue in this case. The problem is that defendants' definition of "wealth" "profit margin" is both vague and unreasonably broad.

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[105] *Id.* at 13.

[106] Ex. 95, *Reeves v. Wyeth*, Trial Tr. at 3141:18-3142:22 (Sept. 8, 2006); Ex. 96, *Rush v. Wyeth*,Trial Tr. at 2868:15-2870:2 (Feb. 12, 2007); Ex. 97, *Scroggin v. Wyeth*, Trial Tr. at 2176:3-2180:12 (Feb. 19, 2008); Ex. 98, *Rowatt v. Wyeth*,Trial Tr. at 4884:17-4888:3, Vol. XIX (Oct. 5, 2007); Ex. 99, *Kendall v. Wyeth*, Trial Tr. at 10:22-12:8 (Nov. 16, 2009 p.m.).

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These terms could potentially touch on a whole host of issues that are directly relevant. Accordingly, plaintiff asks the Court to deny the motion regarding "net worth" as moot and deny the motion as to the remaining issues because they were not properly addressed in their opening motion. It does no good for defendants to clarify the issues it seeks to exclude with more precision in their Reply because plaintiffs will not have an opportunity to respond.

A. Evidence of defendants' wealth is relevant to its ability to fund studies.

Central to plaintiffs' claims is defendants' failure to conduct adequate safety studies on the breast cancer risk of their E+P drugs during the 30+ years they were on the market. Although Premarin was the top selling drug in the country for much of this time, and the "Premarin family" yielded $2 billion in sales, defendants chose not to invest a relatively small amount of money on studies to address the breast cancer concerns raised by the FDA and scientists. Evidence of defendants' profitability, sales and amounts budgeted for research versus marketing and sales are strongly relevant to show the practicality and feasibility to conduct breast cancer studies on E+P, as well as defendants' priorities in choosing not to pursue this research. In short, this evidence goes to the very core of the feasibility of such measures. It also reflects the unreasonableness of defendants' conduct in the choices they made to avoid research in favor of spending heavily on public relations to suppress negative information on their drugs.

How defendants' employees were compensated by defendants is similarly relevant in assessing the reasonableness of defendants' priorities and resources in pushing the benefits of E+P and downplaying the drugs' risks. For instance, sales representatives have testified in previous trials that they were compensated with incentive bonuses based on E+P sales. This pressure influenced how they promoted E+P.

Defendants' marketing strategies could also conceivably encompass "wealth." Among these is Wyeth's campaign to "dismiss and distract" the medical community and patients to skew the risk/benefit profile of E+P. Likewise, Wyeth's decision to spend substantial sums on ghostwriting reflects the low to nonexistent priority it placed on funding original research on

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pressing safety issues. Also implicit in this evidence is the company's decision to invest its resources in a massive public relations effort. Another category of admissible evidence defendants would exclude under the guise of "wealth" is the rise and fall in Premarin sales as a result of the endometrial cancer epidemic. Sales for E+P shot up in the 1980s and 1990s after Wyeth and Upjohn promoted their drugs in combination. In 2002, when the media reported that the WHI was halted due to breast cancer and other side effects, sales of E+P plummeted. So, too, did the breast cancer rate. Certainly, this evidence is highly relevant, and it has routinely been admitted at trial.[107]

B. The evidence is admissible for impeachment purposes.

Plaintiffs do not intend to question defendants' executives about their salaries or compensation packages. But on occasion, defendants have opened the door to such evidence, particularly through the testimony of its employees whom defendants have paid to appear at trial as "litigation consultants" in the duel capacity of fact and expert witnesses. If so, plaintiffs should be permitted to impeach them by asking how much defendants paid them for their consulting services. The court allowed plaintiffs to impeach witnesses with this evidence in *Rowatt v. Wyeth.*[108] Furthermore, plaintiffs anticipate defendants will open the door by telling the jury that they have spent millions of dollars on research on HRT and in the field of women's health generally. If so, plaintiffs should be permitted to introduce evidence of defendants' profits, profit margins and salaries to put that information in its proper context.

Defendants have not met their burden of justifying the exclusion of any financial evidence other than net worth, which plaintiffs have agreed not to introduce at trial. Other relevant evidence of sales, budgets, and profits bear directly on the feasibility for defendants to conduct breast cancer studies on E+P, as well as the reasonableness of their choice to misinform

[107] *See, e.g.*, Ex. 100, *Singleton v. Wyeth*,Trial Tr. at 13:10-24 (Jan. 21, 2010 a.m.) (denying motions to exclude sales and amounts budgeted for research and marketing).

[108] Ex. 101, *Rowatt v. Wyeth*, Trial Tr. at 3262-63 (Sept. 27, 2007).

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the medical community about risks in favor of expanding the E+P market. This evidence is highly relevant and not unfairly prejudicial. It should be admitted.

D23. References to the Absence of a Corporate Representative at Trial

Plaintiffs oppose this motion because it is both misleading and unfair. At first glance, defendants' motion initially seems reasonable enough. It implies that there may be one of many corporate representatives defendants did not call to testify because circumstances prevented them from attending part or all of the trial. That is not the case here. Even though they have disclosed nine current or former employees as potential fact/expert trial witnesses in this case, defendants have recently made the strategic decision not to call any corporate representative at trial to testify on their behalf. Their purpose is to prevent plaintiffs from cross-examining the defendants' representatives with evidence of the companies' liability. Defendants know that without a live witness to put on the stand before the jury, the plaintiffs will not be able to present their liability evidence effectively. Instead, plaintiffs will be forced to present documents through their own regulatory experts, play hours of videotaped depositions and/or read from trial transcripts. Of course, it is defendants' prerogative not to call a corporate representative in person, but this tactic should not permit defendants to gain an unfair advantage. Plaintiffs should be entitled to point out to the jury that defendants chose not to bring corporate witnesses to trial for plaintiffs to cross-examine. As explained in plaintiffs' Motion to Compel, principles of fairness and judicial efficiency dictate that defendants make its key corporate representatives whom they have retained as "litigation consultants" available to testify at trial, either in person or by live videoconferencing. If they do, plaintiffs will not comment on the absence of any particular corporate witness.

D24. Other HT Claims and Lawsuits

Plaintiffs generally agree that all parties should be prohibited from discussing other claimants or the results of other HRT lawsuits. But defendants' motion is too broad. First, it

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would potentially exclude evidence of causation, which necessarily involves references to human epidemiological studies whose results show that E+P caused women who took it to develop breast cancer, including the number of breast cancer cases science has attributed to E+P. Second, the evidence is admissible for impeachment purposes. Assuredly, defendants' counsel will question plaintiffs' expert witnesses at trial about the number of times they have testified in the HRT litigation and other lawsuits, the amount of money they have made testifying, any contradictory testimony they have given in other HRT depositions or trials, and whether their opinions are always the same. Accordingly, plaintiffs are entitled to cross-examine defendants' expert witnesses on those same issues.

Third, if defendants open the door – as they often do – by telling the jury that it manufactures many drugs that save lives or are household names, plaintiffs should be allowed to counterbalance such testimony by presenting evidence of defendants' bad drugs that have killed or injured countless people worldwide. Likewise, if defendants tell the jury they always follow FDA regulations and behave as "good citizens," plaintiffs should be permitted to establish that defendants have repeatedly violated those regulations and paid enormous fines for doing so. By placing their character at issue, defendants create a two-way street.

DATED this 16th day of September, 2011.

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